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(54) Title: STABLE DOSAGE FORMS COMPRISING ATORVASTATIN CALCIUM

(57) Abstract: Solid compositions for oral administration comprising atorvastatin calcium and a sodium or potassium compound, for which an aqueous dispersion is capable of producing a pH above 11.

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STABLE DOSAGE FORMS COMPRISING ATORVASTATIN CALCIUMFIELD OF INVENTION

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This invention relates to solid pharmaceutical compositions for oral administration comprising atorvastatin calcium, and improvement of the stability of such compositions.

10 BACKGROUND OF THE INVENTION

Atorvastatin is a synthetic lipid-lowering agent, and is disclosed and claimed in U.S. patent 5273995.

15 Tablets comprising atorvastatin as the hemi-calcium salt (known as atorvastatin calcium) are sold in the United States as elsewhere under the tradename Lipitor™.

Atorvastatin is a member of a class of compounds known as "statins". These
20 compounds are HMG-CoA reductase inhibitors, and are used as antihypercholesterolemic agents.

Some of these compounds and, in particular, fluvastatin, pravastatin and atorvastatin, have in their molecule a non-esterified hydroxy acid moiety, and
25 thus will form basic salts, such as sodium or calcium salts. When these compounds are in the acid form, they are relatively unstable and are prone to degradation into the corresponding lactones.

It is known from the prior art that stable compositions comprising such
30 compounds can be made either by using these compounds in the form of basic salts, or alternatively, if the acid form is used, including in the composition a basic excipient so as to keep the compound in a basic environment.

™ - Registered trademark.

There are several such prior art publications that deal with stabilization of statins having a non-esterified hydroxy acid moiety.

- 5 U.S. patent 5180589 deals specifically with pravastatin. The disclosure explains that stability of pravastatin in a composition may be improved by including a basifying agent to raise the pH of an aqueous dispersion of the composition to at least 9 and preferably at least 9.5. Nine examples are given along with data which confirms that, in each example, inclusion of magnesium
10 oxide as basifying agent inhibits conversion of the pravastatin to the lactone. The disclosure deals only with pravastatin in its acid form, and not with basic salts of pravastatin such as pravastatin sodium. Pravastatin sodium already being basic, does not require inclusion of a basifying agent in the tablet to improve stability, so long as the tablet contains no acidic excipient (inactive
15 ingredient). This publication makes no mention of atorvastatin calcium.

- Similarly, U.S. patent 5356896 relates to stabilization of solid compositions of fluvastatin against lactone formation by inclusion of a basifying agent so that an aqueous dispersion of the composition will have a pH of at least 8. The
20 disclosure and claims of this patent appear to confuse fluvastatin with its basic salts, and in particular appear to confuse fluvastatin with fluvastatin sodium. All of the examples in the disclosure show compositions which contain, as the active drug, fluvastatin and not fluvastatin sodium, and the examples confirm that compositions which comprise fluvastatin along with a basifying agent are
25 stable. However, all of the claims of this patent are limited to compositions which comprise the drug in the form of a basic salt and not the acid form. Moreover, when the active ingredient is fluvastatin sodium, and not fluvastatin, compositions are stable without the inclusion of a basifying agent, so long as the compositions do not include an acidic excipient. A basifying
30 agent is thus not needed for stability in the case of fluvastatin sodium. It thus appears that the claims erroneously state the drug to be in the form of basic salt, whereas the invention, if any, relates to the drug in the form of the

hydroxy acid. Again, this publication makes no reference to atorvastatin calcium.

- 5 WO 00/35425 discloses compositions comprising an active substance that is a HMG-CoA reductase inhibitor, wherein that active substance is one which is capable of providing a pH in the range of 7 to 11. The term "active substance" is defined as meaning the HMG-CoA reductase inhibitor alone or a mixture thereof with a small amount of a buffering agent. The essence of the
10 invention is that, by using an active substance which provides a pH in the range of 7 to 11, it is possible to achieve improved stability even if the final composition in which it is contained exhibits pH below 9. In other words, by creating an environment locally within each particle of the active substance such that a dispersion of such particles in water would have a pH of 7 to 11, it
15 is not necessary that the entire mass of the composition be highly basic.

- WO 00/35425 has only six examples. The first five all comprise pravastatin sodium as the active drug and the sixth comprises atorvastatin calcium along with dibasic sodium phosphate as buffering agent. The concluding paragraph
20 of the disclosure states that the compositions of all six examples provide excellent stability, with essentially no degradation of the pravastatin or atorvastatin observed. However, as aforesaid, pravastatin sodium is a basic salt and does not require further stabilization in the absence of an acid, so that it is not surprising that the composition of examples 1 to 5 are stable.
25 Moreover, with respect to example 6, as will be explained hereafter, while atorvastatin calcium is stable against conversion to the lactone in the absence of an acid, it is prone to other types of degradation, and in particular oxidation, even at pH of 7 to 11. It is thus more difficult to provide stable compositions for atorvastatin calcium than for pravastatin sodium or fluvastatin sodium. It
30 thus appears that the statement in WO 00/35425 that the composition of example 6 is stable is likely erroneous. It may be that not all degradation products were measured, but only the lactone.

- U.S. patent application 2002/0035142 discloses stabilized compositions
35 comprising a statin that is a hydroxy acid or salt thereof and a stabilizing

amount of an amido-group containing polymer or an amino-group containing polymer. The compositions are said to provide stability against lactone formation. However, where the active ingredient is atorvastatin calcium, such compositions will not provide good stability against types of degradation other
5 than lactone formation.

As aforesaid, atorvastatin calcium is disclosed in U.S. patent 5273995. The processes of this patent produce atorvastatin calcium in amorphous form. Because atorvastatin calcium is a basic salt of atorvastatin, like pravastatin
10 sodium and fluvastatin sodium, it is not unstable against formation of the lactone unless mixed with other acidic compounds. However, it is more prone than pravastatin sodium and fluvastatin sodium to other types of degradation, including oxidation, even as the calcium salt.

15 U.S. patent No. 5969156 teaches new crystalline forms of atorvastatin calcium which are designated as Form I, Form II, Form IV, and are said to be more stable than the amorphous form. Lipitor™ tablets comprise atorvastatin sodium in crystalline Form I.

20 U.S. patent 6126971 relates specifically to stable solid dosage forms comprising atorvastatin calcium. The disclosure confirms that this compound is unstable in that it is susceptible to heat, moisture, low pH environment and light; and that in an acid environment, in particular, the hydroxy acid will degrade to lactone. Since the calcium salt is basic and not acidic,
25 compositions comprising atorvastatin calcium do not require stabilizing against formation of the lactone, so long as the composition does not comprise an acidic excipient. However, as aforesaid, atorvastatin calcium is still unstable to other types of degradation even in the absence of an acid.

30 U.S. patent 6126971 teaches that compositions comprising atorvastatin calcium, even in the absence of an acidic excipient, will exhibit improved stability if the composition comprises at least one excipient that is also a salt of an alkaline earth metal such as calcium or magnesium. All of the examples
35 in this patent comprise atorvastatin calcium as the active ingredient, and

calcium carbonate as the stabilizer. The test data in the disclosure confirms that tablets comprising calcium carbonate are more stable than tablets without calcium carbonate.

- 5 U.S. patent 6126971 thus teaches that, when atorvastatin is in the form of the calcium salt (calcium being an alkaline earth metal), and even in the absence of an acidic ingredient, stability is improved by inclusion of an excipient that is another salt of an alkaline earth metal. This patent thus leads the reader to conclude that, for atorvastatin calcium formulations, metal salts other than
10 those of alkaline earth metals are either ineffective as stabilizers or are less effective as stabilizers than alkaline earth metal salts.

The disclosure of U.S. patent 6126971, does not specify whether the atorvastatin calcium being in the examples used is the amorphous form or
15 one of the crystalline forms disclosed in U.S. patent 5969156. However, as Lipitor™ tablets contain crystalline Form I, which is the most stable form, it appears that the atorvastatin calcium used in the examples is crystalline Form I.

- 20 It has been found when the atorvastatin calcium is in amorphous form, the compositions within the scope of U.S. patent 6126971 do not enable good stability. Moreover, even Lipitor™ tablets exhibit slow degradation of the atorvastatin calcium content.

- 25 In view of this prior art, one objective of the present invention is to enable solid compositions for oral administration comprising atorvastatin calcium that are stable, even when the atorvastatin calcium is an amorphous form. Another objective of the invention is to enable atorvastatin calcium tablets that
30 are stable without comprising an excipient that is an alkaline earth metal salt. Another objective of the invention is to enable atorvastatin calcium tablets that are more stable than Lipitor™ tablets.

DESCRIPTION OF THE INVENTION

As aforesaid, WO 00/35425 teaches that atorvastatin sodium is best stabilized by incorporating it into particles for which the pH of an aqueous dispersion is
5 between 7 and 11; and U.S. patent 6126971 teaches that atorvastatin calcium is best stabilized by including in the composition an excipient that is also an alkaline earth metal salt (as is atorvastatin calcium itself).

In light of this prior art, it has now been surprisingly found that atorvastatin
10 calcium is best stabilized against degradation, including oxidation, by incorporating a basic sodium or potassium compound along with the atorvastatin calcium in the composition, or in particles within the composition, such that an aqueous dispersion of the composition or of the particles is capable of providing a pH above 11.

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Accordingly, compositions within the scope of the present invention will comprise atorvastatin calcium and at least one sodium or potassium compound, such that either:

- 20 i) an aqueous dispersion of the composition is capable of producing a pH of above 11; or

- ii) the composition comprises particles which further comprise said atorvastatin calcium and said sodium or potassium compound, and an aqueous dispersion of said particles is capable of producing a pH of above 11.

The sodium or potassium compound may be a hydroxide or a salt of a weak acid. Suitable compounds will include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, tribasic sodium phosphate, and tribasic potassium phosphate. The sodium or potassium compound may be either anhydrous or hydrated.

Especially preferred are tribasic sodium phosphate and tribasic potassium phosphate. Most preferred is tribasic sodium phosphate.

The composition will preferably be tablets.

The composition will also preferably include one or more excipients other than the sodium or potassium compound.

Such excipients may include, for example, any or all of:

- i) A binder, such as microcrystalline cellulose.
- ii) A disintegrant, such as starch, croscarmellose sodium, sodium starch glycolate, or crospovidone.
- iii) A lubricant, such as magnesium stearate.
- iv) A glidant, such as colloidal silicon dioxide.

When the composition is in the form of tablets, the tablets may be made by a direct compression process, wherein the ingredients are mixed together in dry form and the mixture is directly compressed into tablets.

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If the powder mixture does not flow well enough for direct compression, then the flow may be improved by either a wet granulation or a dry granulation process.

- 10 In a wet granulation process, ingredients are made into a wet mass using water or an organic solvent, in which a binder may optionally be dissolved, and the wet mass is then dried and milled into free-flowing granules. Alternatively, flow may be improved by a dry granulation process, also known as compaction or slugging, in which a mixture of ingredients is first
- 15 compressed into compacted material, which is then milled into granules, which are then recompressed into the final tablets.

The invention will be better understood from the following examples which are meant to be illustrative and not limiting the scope of the invention.

20

EXAMPLES

Examples 1 to 4 were made as follows:

Example No.:	1	2	3	4
25 Atorvastatin Calcium Amorphous	5.4	5.4	5.4	5.4
30 Sodium Carbonate Monohydrate	124.6	0	0	0
Sodium Citrate Dihydrate	0	124.6	0	0
35 Sodium Phosphate Dibasic Anhydrous	0	0	124.6	0
Sodium Phosphate Tribasic, Anhydrous	0	0	0	124.6
40	130.	130.	130.	130.

For each of the four examples, the ingredients were mixed in the proportion shown. The mixture was then compressed into slugs using a tablet press. The slugs were then ground up into granules, which are particles comprising atorvastatin calcium and the sodium compound. The granules were

5 recompressed into tablets at a weight of 130 mg each. Each tablet thus contained about 5.4 mg of atorvastatin calcium, which is equivalent to about 5 mg of atorvastatin, allowing for a water content of about 4 percent.

Sample tablets of each of the four examples and also sample tablets of

10 Lipitor™ were then stored at 60°C for two weeks. Samples of each, along with samples that had been kept at room temperature, were then tested for degradation products by a High Performance Liquid Chromatographic (HPLC) method. The amounts by which the total degradation products in the samples stored at 60°C exceeded the total degradation products in the samples stored

15 at room temperature were as follows:

	<u>Example #</u>	<u>Stabilizer</u>	<u>Increase in Degradation Products at 60°C Levels</u>
20	1	Sodium carbonate Monohydrate	1.16%
	2	Sodium citrate Dihydrate	1.27%
	3	Sodium phosphate dibasic Anhydrous	1.52%
	4	Tribasic sodium phosphate Anhydrous	0
	Lipitor™	Calcium carbonate	0.18%

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For the tablets of examples 1 and 4, the pH of an aqueous dispersion (and also the pH of an aqueous dispersion of the granules from which they were made) exceeds 11; whereas for examples 2 and 3 the pH is less than 11. Examples 1 and 4 are thus examples of the present invention; examples 2

30 and 3 are not examples of the present invention, but are included for comparison purposes.

It can be seen that the stability of the tablets of examples 1 and 4 is superior

35 to that of examples 2 and 3. Also, and very surprisingly, the stabilizing effect of tribasic sodium phosphate in example 4 is even better than that of sodium carbonate, in example 1, despite the fact that the pH of the aqueous

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dispersions for both exceed 11. Use of tribasic sodium phosphate in compositions of the present invention thus enables stability even better than that of Lipitor™.

- 5 As tribasic potassium phosphate is very similar to tribasic sodium phosphate in physico-chemical characteristics, it may be concluded that tribasic sodium phosphate and tribasic potassium phosphate are both especially preferred as stabilizers for atorvastatin calcium, in compositions of the present invention.

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CLAIMS

1. A solid composition for oral administration comprising atorvastatin
5 calcium and at least one sodium or potassium compound, such that
either an aqueous dispersion of the composition is capable of providing
a pH above 11, or alternatively the composition comprises particles
which comprise said atorvastatin calcium and said sodium or
potassium compound, and an aqueous dispersion of said particles is
10 capable of producing a pH above 11.
2. A composition of claim 1 wherein the atorvastatin calcium is
amorphous.
- 15 3. A composition of claim 1 or 2 that is a tablet.
4. A composition of any of claims 1 to 3 wherein the sodium or potassium
compound is sodium hydroxide.
- 20 5. A composition of any of claims 1 to 3 wherein the sodium or potassium
compound is potassium hydroxide.
6. A composition of any of claims 1 to 3 wherein the sodium or potassium
compound is sodium carbonate.
- 25 7. A composition of any of claims 1 to 3 wherein the sodium or potassium
compound is potassium carbonate.
8. A composition of any of claims 1 to 3 wherein the sodium or potassium
30 compound is selected from tribasic sodium phosphate and tribasic
potassium phosphate.
9. A composition of claim 8 wherein the sodium or potassium compound
35 is tribasic sodium phosphate.

10. A composition of claim 8 wherein the sodium or potassium compound is tribasic potassium phosphate.
- 5 11. A solid composition for oral administration comprising atorvastatin calcium and either tribasic sodium phosphate or tribasic potassium phosphate.
- 10 12. A composition of claim 11 wherein the atorvastatin calcium is amorphous.
13. A composition of claim 11 or 12 comprising tribasic sodium phosphate.
- 15 14. A composition of claim 11 or 12 comprising tribasic potassium phosphate.
15. A composition of any of claims 11 to 14 in the form of a tablet.

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INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/40 A61K47/02 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

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INTERNATIONAL SEARCH REPORT

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